

# Management of Charcot neuroarthropathy

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**Charcot neuroarthropathy of the lower limb is a serious complication of diabetes, which can result in significant deformity that can lead to lower-limb amputation. Here, the authors discuss the pathogenesis, classification and management of this condition with reference to the most recent literature.**

Charcot neuroarthropathy (CN) is a relatively rare condition that is poorly understood and commonly goes unrecognised until symptoms are severe and foot deformity is already established (Caputo et al, 1998). CN is a progressive condition that is characterised by acute fractures, subluxations and joint destruction that can, without diagnosis and management, result in severe foot deformity (Frykberg et al, 2006).

In addition to the morbidity associated with foot deformity, individuals with CN are also at increased risk of ulceration, placing this group at increased risk of lower-limb amputation (Rajbhandari et al, 2002). Once diagnosed, CN is a challenging condition to manage and requires holistic management by a multidisciplinary team to prevent or limit the development of associated complications (Rajbhandari et al, 2002).

## Pathogenesis

The exact pathogenesis of CN is unclear. There are two well-described theories for the aetiology of CN: the neurotraumatic and neurovascular theories. It is widely held that both the neurotraumatic and neurovascular theories are likely to contribute to CN.

## Neurotraumatic theory

According to the neurotraumatic theory, CN is the result of repetitive micro-trauma to the foot or ankle resulting from the absence of protective sensation. Micro-trauma gives rise to stress fractures, ligamentous laxity and joint instability. Due to the loss of protective sensation, the affected person may not experience symptoms and therefore continue to use the affected foot and fail to seek medical help. With continued weight bearing, further degeneration of the bones and joints occurs, resulting in CN (Frykberg and Mendezsoon, 2000; Armstrong and Peters, 2002; deSouza, 2008).

## Neurovascular theory

The neurovascular theory holds that autonomic neuropathy causes an increase in blood flow to the foot, which leads to hyperaemic bone resorption – a net increase in osteoclastic activity over osteoblastic activity (Rajbhandari et al, 2002). The resorption of bone leads to bone loss and weakening of the supporting structures, predisposing the osteopenic bone to the development of CN (Frykberg and Mendezsoon, 2000; Armstrong and Peters, 2002).

## Article points

1. Charcot neuroarthropathy (CN) is a major cause of morbidity and is associated with an increased risk of developing foot deformity, recurrent ulceration and the need for lower limb amputation.
2. Early diagnosis and immediate treatment can minimise the morbidity and complications associated with CN.
3. New evidence suggests that combining imaging techniques offers the highest diagnostic accuracy in differentiating osteomyelitis from CN.
4. The principle aim of treatment is to protect foot architecture during the inflammatory and destructive stages until the quiescent phase begins.

## Keywords

- Charcot neuroarthropathy
- Foot deformity
- Total-contact cast

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Page points

1. A theory on the pathogenesis of Charcot neuroarthropathy (CN) concerning pro-inflammatory cytokines and the RANKL-NF-kB pathway has achieved growing interest.
2. Estimates of the prevalence of CN vary widely, with between 0.8 and 7.5% of people with diabetes and neuropathy believed to have the condition.
3. The Eichenholtz classification system is most commonly used to identify the stages of CN.

Inflammatory factors

Both the neurotraumatic and neurovascular theories are supported in the literature; however, an alternative theory concerning pro-inflammatory cytokines and the RANKL-NF-kB pathway has achieved growing interest. In those with diabetes and peripheral neuropathy, Jeffcoate et al (2005) suggest that CN is due to an exaggerated inflammatory response to trauma. In such cases, trauma initiates a positive feedback cycle, whereby the increased release of pro-inflammatory cytokines, including tumour necrosis factor-alpha and interleukin-1-beta, leads to the increased expression of the receptor activator of nuclear transcription factor-kappa B (RANKL). This causes the activation of NF-kB, which in turn increases osteoclast maturation and subsequent osteolysis, ultimately leading acute CN.

Epidemiology

Estimates of the prevalence of CN vary widely, with missed diagnoses and variable descriptions of the condition likely contributors to the variation (Wukich and Sung, 2009). Between 0.8 and 7.5% of people with diabetes and neuropathy are believed to have the condition, with

between 9 and 35% of them having bilateral involvement (Harrelson, 1993; Armstrong et al, 1997a). The majority of cases of CN occur in the midfoot, and almost 50% with an associated plantar ulcer (Harrelson, 1993).

Classification

The Eichenholtz (1966) classification system is most commonly used to identify the stages of CN (Armstrong and Peters, 2002; Frykberg et al, 2006; de Souza, 2008). Eichenholtz classified CN into three stages based on radiographic findings: (i) development; (ii) coalescence, and; (iii) reconstructive (Table 1). In clinical practice, the development stage is considered to be the acute phase, while the coalescent and reconstructive stages are considered quiescent or chronic.

More recently, an earlier stage – stage 0 – was added to the Eichenholtz classification system that corresponds to the initial inflammatory phase when radiographic changes on plain X-ray are not evident but may be seen on magnetic resonance imaging (MRI; Armstrong and Peters, 2002; Nubé et al, 2002; Yu and Hudson, 2002). In practice, stage 0 may be hard to distinguish from stage 1, but it is at stage 0 when deformity and radiological changes on plain

**Table 1. Modified Eichenholtz classification for Charcot neuroarthropathy and associated clinical features (Armstrong and Peters, 2002; Yu and Hudson, 2002; Frykberg et al, 2006).**

Stage	Radiographic changes	Features†
0	No radiographic changes on plain X-ray; changes evident on magnetic resonance imaging	Sudden onset of swelling of the foot, ankle or leg; erythema; increase in temperature (generally ≥2°C in comparison with the contralateral foot); bounding pedal pulses; pre-existing loss of protective sensation; diminished or absent deep tendon reflexes; new onset of pain‡
1. Development	Diffuse swelling; joint laxity; subluxation; dislocation; fine peri-articular fragmentation; debris formation	As for stage 0; foot deformity§
2. Coalescence	Absorption of osseous debris; fusion of larger fragments; dramatic sclerosis	Decrease in skin temperature; decrease in erythema; decrease in swelling; foot deformity§
3. Reconstructive	Osseous remodeling; new bone formation	The increase in temperature has subsided; swelling has subsided; foot deformity§

†Please note that the absence of any of these features does not necessarily exclude a diagnosis of Charcot neuroarthropathy; ‡the level of pain an individual would experience throughout these stages is much less than what would be normally expected for the severity of the clinical and/or radiographic findings; §if the CN foot is detected early and prompt immobilisation is implemented this may limit or prevent the development of foot deformity.

**Page points**

1. Debate exists regarding which imaging modality is best for differentiating acute Charcot neuroarthropathy (CN) from osteomyelitis in the presence of an ulcer.
2. Current evidence suggests that magnetic resonance imaging combined with plain X-rays offer the highest diagnostic accuracy and is therefore the preferred diagnostic test.
3. A handheld infrared dermal thermometer can be used to objectively and quantitatively assess temperature differences between the CN affected and contralateral foot.

X-ray are yet to develop that treatment is likely to have its greatest chance of preventing deformity. However, due to the rarity of CN, individuals with a stage 0 foot are often misdiagnosed with gout, deep vein thrombosis or cellulitis, leading to a delay in the recognition and treatment of CN (Rajbhandari et al, 2002; Yu and Hudson, 2002).

Debate exists regarding which imaging modality is best for differentiating acute CN from osteomyelitis in the presence of an ulcer. Differentiating between these two entities using plain X-rays alone may be difficult. Berendt and Lipsky (2004) and Rogers and Bevilacqua (2008) have stated that osteomyelitis is related to an ulcer, is usually confined to one bone and generally occurs in the forefoot or calcaneus. CN involves multiple bones, may not relate to the ulcer and is more likely to occur in the midfoot. Consideration of these features may help in differentiating CN from osteomyelitis using plain X-rays. For a diagnosis to be made, the appearances and distributions of the abnormalities, and their correlation with the clinical features, need to be established (*Table 2*).

The use of white blood cell scans were once recommended for the differentiation of osteomyelitis from CN, however there is current evidence to suggest that MRI combined with plain X-rays offer the highest diagnostic accuracy and is therefore the preferred diagnostic test (Berendt and Lipsky, 2004; Tan and Teh, 2007; Rogers and Bevilacqua, 2008).

**Diagnosis and monitoring of CN**

In clinical practice, plain X-rays and the use of infrared dermal thermometry for

measuring skin temperatures are useful tools that are important adjuncts to clinical examination as they assist in detecting, staging and monitoring CN (Rajbhandari et al, 2002).

X-rays should be taken as soon as possible after presentation as they can serve as a baseline for ongoing comparisons (*Figure 1*). In the early stages of CN, X-rays may appear normal or demonstrate only subtle changes. However, if clinical suspicion is high, further imaging with MRI should be undertaken.

X-rays should be repeated within 2–3 weeks of presentation as bone destruction becomes more evident over time (Armstrong and Peters, 2002; Perrin et al, 2010). The literature varies as to how often follow up X-rays should be performed. Sommer and Lee (2001) and Yu and Hudson (2002) propose that X-rays should be taken every 4–6 weeks, while Fabrin et al (2000) suggest every 6–12 weeks. A number of authors suggest that films should be taken more frequently if there is an acute change within the architecture of the foot or ankle (Sommer and Lee, 2001; Yu and Hudson, 2002).

A handheld infrared dermal thermometer can be used to objectively and quantitatively assess temperature differences between the CN affected and contralateral foot. The literature suggests that foot temperatures should be measured and recorded at every follow-up visit and compared with the contralateral limb (Armstrong et al, 1997b; Nubé et al, 2002).

Armstrong and Lavery (1997) found that elevated skin temperatures correlated with the location of CN and that the temperatures decreased as CN progressed from the acute

**Table 2. Features that assist in the differential diagnosis of Charcot neuroarthropathy from osteomyelitis on magnetic resonance imaging (Berendt and Lipsky, 2004; Tan and Teh, 2007).**

Feature	Charcot neuroarthropathy	Osteomyelitis
Bone marrow signal change	Acute: Mimics osteomyelitis Chronic: Low on T1 and T2	High signal on T2 Low on T1
Bone marrow oedema pattern	Periarticular	Diffuse
Distribution	Several joints and bones involved	Focal involvement (generally one bone)
Common site of involvement	Midfoot	Toes, metatarsals, calcaneus

to post-acute phase. The sites at which to measure the temperature of the foot varies among reports the literature, with many authors providing their own suggestions and advice. Studies by Armstrong and Lavery (1997) and Armstrong et al (1997b) recorded temperature measurements from nine sites on the foot (the hallux, first, third and fifth metatarsal heads, first metatarsocuneiform joint, talonavicular joint, cuboid, heel and anterior ankle). McGill et al (2000) recorded the site at which the infrared dermal thermometry measured the highest temperature and subsequent measurements were taken at the same location at each follow-up visit. Whereas Bernstan and Motko (2008) suggested that measurements be taken over the medial and lateral arch, medial and lateral malleoli, dorsum of the foot and the tibial crest.

Management of bilateral CN can be challenging. Dermal thermometry is less effective in providing clinically useful information. Bilateral total-contact casting (TCC) would be the preferred treatment in such cases, but, in practice, this would not be an appropriate course of treatment for the majority of individuals.

### Management of CN

#### Conservative management

Recommended treatment for CN is immobilisation and non-weightbearing of the affected foot during the acute phase. The aim of treatment is to protect and rest the affected foot during the inflammatory and destructive stages, until the quiescent phase begins. This, in turn, may prevent or limit the development of permanent foot deformity so that, ultimately, the foot can be accommodated in footwear (de Souza, 2008).

The gold standard treatment for acute CN is TCC (Armstrong et al, 1997a; Armstrong and Lavery, 1998; Frykberg et al, 2006). The initial cast should be changed after 1 week to accommodate the decrease in oedema. Subsequent casts can generally be changed fortnightly, dependent on cast comfort and integrity (Frykberg et al, 2006). In those

cases with concurrent active ulceration, casts should be changed weekly to allow for appropriate wound care. The cast is discontinued once the quiescence phase is reached, based on clinical, radiographic and dermal thermometric signs.

The post-acute phase of CN involves progression from a TCC to removable walker or Charcot restraint orthotic walker (CROW), and finally to accommodative footwear. Armstrong et al (1997a) proposed that removable walkers should be used to ease the transition from TCC to accommodative footwear and this has become widely accepted in practice. It is suggested that the transition from

#### Page points

1. Recommended treatment for Charcot neuroarthropathy (CN) is immobilisation and non-weightbearing of the affected foot.
2. The gold standard treatment for acute CN is total-contact casting.



*Figure 1. Plain X-rays of an 80-year-old man with Charcot neuroarthropathy (CN) of the right foot over a 12-month period. (a) An oblique radiograph that demonstrates an Eichenholtz Stage 1 CN foot (see Table 1). Minimally displaced fractures of the base of the third and fourth metatarsals can be seen. (b) An anteroposterior radiograph, taken 6 weeks after the initial radiograph, demonstrates a Lisfranc fracture, dislocation involving the bases of the second, third and fourth metatarsals. (c) An oblique radiograph showing moderate sclerosis of the medial cuneiform. (d) An anteroposterior radiograph of the foot 12 months after the initial radiograph. Note the healed Lisfranc fracture.*

### Page points

1. Many clinicians recommend strict non-weight-bearing and immobilisation; however, the decision as to whether the individual should be weight-bearing through a cast, with assisting devices, during the acute phase remains open to debate.
2. Controversy exists regarding the timing and risks of performing corrective surgery in individuals with Charcot neuroarthropathy (CN)-induced deformity.
3. Over the past decade there has been interest surrounding the reduction in disease activity and bone turnover by using bisphosphonates in the management of acute CN.

TCC to removable walker or CROW is generally made when the temperature differential between the affected foot and the contralateral foot is less than 1°C for at least 2 consecutive weeks. The transition from removable walker to accommodative footwear is based on 1 month of skin temperature equilibrium ( $\pm 1^\circ\text{C}$ ; Armstrong et al, 1997a; Armstrong and Peters, 2002; Perrin et al, 2010).

The CROW is a useful device for providing immobilisation, oedema control and protection from micro-trauma during the initial period of weight bearing (Morgan et al, 1993). The CROW is a custom made, bivalved total-contact, full-foot enclosure ankle-foot orthosis that can accommodate existing deformities and distribute plantar pressure more evenly (Morgan et al, 1993). A CROW should not be used in the acute CN foot as changes in level of oedema during this phase will compromise its fit.

Many clinicians recommend strict non-weight-bearing and immobilisation with a TCC during the acute phase of CN. However, the decision as to whether the individual should be weight-bearing through the cast, with assisting devices, during the acute phase remains open to debate. Armstrong et al (1997a) and Sinacore (1998) both studied the effects and duration of use of the ambulatory TCC. Sinacore (1998) reported an average time of 3 months of partial weight-bearing in a TCC with assisting devices, whereas Armstrong et al (1997a) reported an average time of 18.5 weeks of TCC before the CN became quiescent.

Both of these studies found the ambulatory TCC to cause no harm and to be an effective method of treatment that would be adequate in most cases. Armstrong et al (1995) studied the effects of the contralateral limb during TCC and found that a three-point gait with crutches may increase the focal pressures on the contralateral limb, exposing it to repetitive stress and ulceration. These results suggest that weight-bearing in a TCC may reduce forces on the contralateral limb when

compared with un-cast walking and three-point walking with crutches (Armstrong et al, 1995).

There are currently no published data that compare long-term outcomes between TCC and non-removable walkers in the management of acute CN.

### Surgical management

If CN is identified in its early stages and an appropriate management plan is implemented, the need for surgical intervention can be avoided. However, controversy exists regarding the timing and risks of performing corrective surgery in individuals with CN-induced deformity.

Most authors agree that surgery is not advisable during the acute CN phase due to the high risk of complications including delayed unions, pseudoarthrosis, infection or hardware failure (Armstrong and Lavery, 1998; Frykberg et al, 2006; Stapleton et al, 2009). These complications are due to the oedema, osteopenia and fragility of bones. Furthermore, there is evidence to suggest that surgery may exacerbate, or act as a stimuli for, CN (Berendt and Lipsky, 2004; Ndip et al, 2008). However, Simon et al (2000) demonstrated successful arthrodesis in all 14 participants with Eichenholtz stage 1 CN of the midfoot. None of the participants had immediate or long-term postoperative complications and all regained their pre-arthropathy level of ambulation. Key reasons cited for their success were improvements in internal fixation techniques and proper protocols for immobilisation. Nevertheless, more studies in larger populations are needed before this type of intervention can be adopted as routine management in acute CN.

### Bisphosphonates

Over the past decade there has been interest surrounding the reduction in disease activity and bone turnover by using bisphosphonates in the management of acute CN. Selby et al (1994) performed pamidronate infusions in six people with diabetes and acute CN.

All participants received six infusions of pamidronate over a 12-week period, at the conclusion of which the authors demonstrated a decrease in skin temperature and a fall in alkaline phosphate activity, indicating a reduction in bone turnover and hence disease activity.

Jude et al (2001) conducted a double-blind randomised controlled trial involving 39 people, each receiving either a single 90-mg infusion of pamidronate or saline (placebo) in addition to the provision of an offloading device. Skin temperatures and markers of bone turnover decreased in both the treated and placebo groups, although to a greater degree in the treatment group. However, the effect of pamidronate was not sustained and the markers for bone turnover returned to normal 6–12 months following the intervention.

More recently, Pitocco et al (2005) conducted a randomised, controlled trial

on the use of oral alendronate in 20 people with acute CN over a 6-month period. This study found significant reductions in serum collagen COOH-terminal telopeptide of type 1 collagen and hydroxyproline, both markers of bone resorption. There is evidence to suggest that pamidronate infusions may be a beneficial adjunctive therapy in reducing the inflammatory process in CN, but whether this yields a final positive outcome, is unclear.

### Conclusion

CN is a potentially debilitating foot condition that requires early diagnosis, careful clinical monitoring and appropriate management to limit or prevent foot deformity and thus reduce the risk of ulceration, loss of function and lower-limb amputation. A high index of suspicion whenever an individual with diabetes

***“Charcot neuroarthropathy is a potentially debilitating foot condition that requires early diagnosis, careful clinical monitoring and appropriate management to limit or prevent foot deformity.”***

***“A high index of suspicion whenever an individual with diabetes presents with a warm, swollen foot in the setting of neuropathy should be maintained by all clinicians.”***

presents with a warm, swollen foot in the setting of neuropathy should be maintained by all clinicians. Individuals who present with suspected CN should be referred for imaging and ongoing management by a high-risk foot service. ■

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